Lasofoxifene Reduced *ESR1* Mutant Allele Fraction and Provided Clinical Benefit versus Fulvestrant in Metastatic Breast Cancer: the ELAINE 1 trial

Massimo A Cristofanilli, MD, FACP[1]; Daniel G Stover, MD[2]; Hope S Rugo, MD[3]; Erika Hamilton, MD[4]; Timothy J Pluard, MD[5]; Donald P McDonnell, PhD[6]; Dominic Carroll[7]; Barry Komm, PhD[8]; Paul V Plourde, MD[7]; David J Portman, MD[7]

[1]Weill Cornell Medicine, New York, NY; [2]Ohio State University, Columbus, OH; [3]University of California, San Francisco, CA; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [5]Saint Luke's Cancer Institute, Kansas City, MO; [6]Duke University, Duke Cancer Institute, Durham, NC; [7]Sermonix Pharmaceuticals, Columbus, OH; [8]Komm Pharma Consulting LLC, San Francisco, CA

Introduction

- Acquired *ESR1* mutations cause endocrine resistance and poor prognosis in ER+/HER2- metastatic breast cancer (mBC)[1-4]
- Preclinically, lasofoxifene (LAS), a selective estrogen receptor modulator (SERM) vs fulvestrant (Fulv), a selective estrogen receptor degrader (SERD)
  - Reduced tumor growth and metastases more in a mBC *ESR1*-mutant (*ESR1*-mut) xenograft model[5]
  - Retained potency, while Fulv, oral SERDs, and other SERMs tested lost potency with greater relative expression of *ESR1*-mut over *ESR1*-wild type (*ESR1*-WT) in BC cells (Figure 1)[6]
- Circulating tumor DNA (ctDNA) analysis has high sensitivity for detecting mutations identified in breast biopsies,[7] with a potential for guiding treatment selection and monitoring outcome[7-9]
  - Fluctuations in ctDNA mutant allele fraction (MAF) may correlate with tumor response;[8,9] although, MAF can change for other reasons (eg, tumor shedding, location, and size)
- The anti-tumor activity of LAS vs Fulv is being evaluated in the phase 2, open-label, randomized ELAINE 1 trial for ER+/HER2- mBC with *ESR1*-mut (NCT03781063)

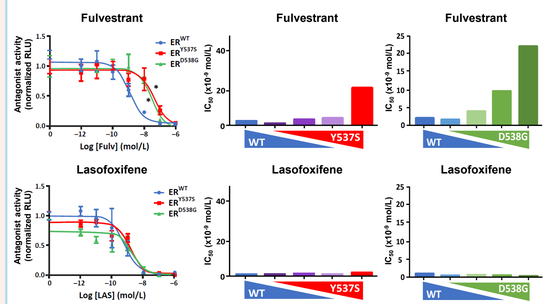
Objectives

- To investigate whether baseline *ESR1*-mut MAF from ctDNA could potentially be associated with clinical response to LAS and Fulv in the ELAINE 1 study
- To explore a potential predictive clinical role of *ESR1*-mut levels

Methods

- Women with ER+/HER2- mBC and *ESR1*-mut ctDNA whose disease progressed on prior (≥12 months) aromatase inhibitors (AIs) plus CDK4/6 inhibitors were randomized to oral LAS 5 mg daily or IM Fulv 500 mg on days 1, 15, and 29, then every 4 weeks, until disease progression/toxicity
- ctDNA was analyzed for *ESR1* mutations by the Sysmex OncoBeam or Sysmex-Inostics SafeSeq assay
- The primary endpoint was progression-free survival (PFS) and secondary endpoints included clinical benefit rate (CBR)
- Association of baseline *ESR1*-mut MAF with CBR at week 24 and changes in MAF from baseline to week 8 were assessed
  - MAF of ≥2% was defined as high

Figure 1. Antagonist potency of Fulv and LAS in breast cancer cells



Adapted from Andreano 2020[6] with permission (copyright © 2020, American Association for Cancer Research).
*Significant differences (P<0.05) of mutant IC_{50}s when compared with that of WT.
Fulv, fulvestrant; LAS, lasofoxifene; WT, wild type.

Results

Patient disposition and baseline characteristics

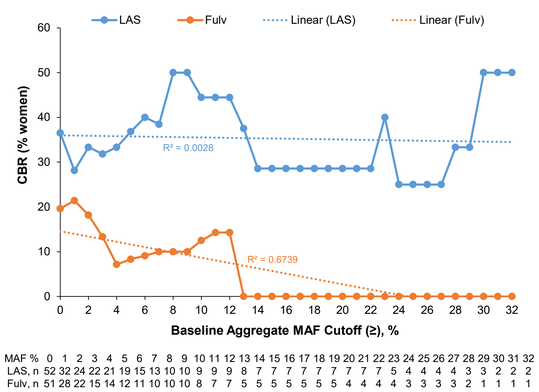
- 103 patients (ITT population) were randomized to LAS (n=52) and Fulv (n=51)
  - To date, most patients experienced disease progression on LAS or Fulv (n=43 in each group)
  - Study discontinuations (other than disease progression) were due to consent withdrawal (LAS vs Fulv: n=2 vs 4), relocation (0 vs 1), investigator decision (2 vs 1), adverse event (1 vs 0; this LAS patient had severe esophagitis and withdrew before dosing), or other causes (0 vs 1)
- Patients had a mean age of 60.8 years; most were white (83%) and had visceral disease (66%; Table 1); prior AI plus CDK4/6i use was for a mean of ~2 years
- Common baseline *ESR1*-mut variants (>10% prevalence) detected were D538G (56%), Y537S (39%), Y537N (29%), E380Q (22%), and Y537C (11%)
  - 56 (54%) patients had polyclonal *ESR1* mutations

Table 1. Baseline demographics and characteristics (ITT population)

	Lasofoxifene (n=52)	Fulvestrant (n=51)
Mean age (range), yrs	61.6 (33–84)	60.1 (38–82)
Race		
White	43 (82.7)	42 (82.4)
Black or African American	6 (11.5)	5 (9.8)
Asian	3 (5.8)	4 (7.8)
Measurable disease, n (%)	38 (73.1)	33 (64.7)
Visceral disease, n (%)	35 (67.3)	33 (64.7)
Chemotherapy in mBC, n (%)	3 (5.8)	3 (5.9)
AI/CDK4/6i, n (%)	52 (100)	51 (100)
Mean duration on AI/CDK4/6i, yrs	2.5	2.2
ESR1 mutation	52 (100)	51 (100)

AI, aromatase inhibitor; CDK4/6i, Cyclin-dependent kinase 4/6 inhibitor; ITT, intent-to-treat.

Figure 2. Clinical benefit rate as a function of baseline *ESR1*-mut MAF cutoff



CBR: proportion of patients with the best overall response being CR, PR, or ≥24 weeks of SD or non-CR/Non-PD.
n: number of patients with aggregate MAF ≥cutoff.
CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; LAS, lasofoxifene; MAF, mutant allele fraction; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Proportion of common *ESR1*-mut variants with decreased MAF from baseline to week 8 as a function of baseline aggregate MAF cutoff

MAF Cutoff	Tx Arm	% (n/N) of *ESR1*-mut variants with MAF decreased					
		D538G	Y537S	Y537N	E380Q	Y537C	Combine
≥0%	LAS	82% (23/28)	87% (13/15)	92% (11/12)	71% (5/7)	100% (6/6)	**85% (58/68)**
	Fulv	39% (7/18)	39% (7/18)	67% (8/12)	56% (5/9)	75% (3/4)	**49% (30/61)**
≥1%	LAS	87% (13/15)	83% (5/6)	100% (4/4)	100% (1/1)	100% (1/1)	89% (24/27)
	Fulv	60% (3/5)	22% (2/9)	25% (1/4)	67% (2/3)	67% (2/3)	42% (10/24)
≥2%	LAS	89% (8/9)	**80% (4/5)**	100% (2/2)	100% (1/1)	100% (1/1)	**89% (16/18)**
	Fulv	67% (2/3)	**14% (1/7)**	0% (0/3)	50% (1/2)	50% (1/2)	**29% (5/17)**
≥5%	LAS	83% (5/6)	100% (2/2)	100% (2/2)	100% (1/1)	N/A	91% (10/11)
	Fulv	50% (1/2)	50% (1/2)	0% (0/2)	0% (0/1)	N/A	29% (2/7)
≥8%	LAS	67% (2/3)	100% (2/2)	100% (1/1)	100% (1/1)	N/A	86% (6/7)
	Fulv	50% (1/2)	0% (0/1)	0% (0/2)	N/A	N/A	20% (1/5)
≥10%	LAS	67% (2/3)	100% (2/2)	100% (1/1)	100% (1/1)	N/A	86% (6/7)
	Fulv	50% (1/2)	0% (0/1)	N/A	N/A	N/A	33% (1/3)

N: number of each respective *ESR1*-mut variant in patients with aggregate MAF ≥cutoff.
n: number of variants with MAF decreased from baseline to week 8.
Fulv, fulvestrant; LAS, lasofoxifene; MAF, mutant allele fraction; NA, not applicable; Tx, treatment.

Correlation of clinical benefit (CB) with *ESR1*-mut MAF cutoff

- PFS (median [95% CI]) was 6.04 (2.82–8.04) months for LAS and 4.04 (2.93–6.04) months for Fulv, with a hazard ratio (HR [95% CI]) of 0.699 (0.434 to 1.125) for LAS vs Fulv (*P*=0.14)
- CBR was 37% (19/52) for LAS and 22% (11/51) for Fulv (*P* =0.12)
- LAS consistently provided superior CB, independent of baseline MAF (Figure 2A)
  - CBR for LAS was maintained across baseline MAF cutoff, whereas CBR for Fulv decreased as baseline MAF cutoff increased
- For the Y537S mutant, CBR increased with LAS but decreased with Fulv as the baseline MAF cutoff increased (Figure 2B)

Changes in MAF for common *ESR1*-muts

- 68 (LAS) and 61 (Fulv) common *ESR1*-mut variants (D538G, Y537S, Y537N, E380Q, and Y537C) were identified in patients with evaluable baseline and week 8 ctDNA
- LAS consistently decreased MAF for a greater proportion of variants irrespective of baseline aggregate MAF cutoff (Table 2)
  - Decreases from baseline to week 8 were observed in 85% of common variants for LAS and 49% for Fulv (Table 2)
- In patients with high baseline aggregate MAF (≥2%), LAS decreased MAF for 89% (16/18) of common *ESR1*-mut variants, while Fulv decreased 29% (5/17) (Table 2)
  - For the difficult-to-treat Y537S mutation, LAS decreased MAF for 80% (4/5) of the variant, while Fulv decreased MAF for 14% (1/7)

Key Takeaways

- In ELAINE 1, LAS but not Fulv consistently provided CB in patients with mBC and *ESR1*-muts, independent of baseline *ESR1*-mut MAF
- LAS consistently decreased MAF for a greater proportion of variants irrespective of baseline aggregate MAF cutoff
- In patients who had high baseline MAF (≥2%), LAS decreased MAF for 89% of common *ESR1*-mut variants, while Fulv decreased 29%

Conclusions

- A higher proportion of *ESR1*-mut variants decreased with LAS versus Fulv (85% vs 49%), including the Y537S variant often associated with Fulv-resistance and worse outcomes,[3] consistent with target engagement
- Baseline MAF may be a surrogate of *ESR1* heterogeneity by measuring relative value of *ESR1*-mut to *ESR1*-WT. It can also indicate higher tumor burden and/or tumor shedding in an endocrine-resistance setting
- LAS but not Fulv consistently provided CB to patients with *ESR1*-muts, independent of high baseline *ESR1*-mut MAF. Moreover, the difference in CB with LAS vs Fulv appeared to be even greater in patients with a higher baseline MAF
- Our results suggest that baseline ctDNA *ESR1*-mut MAF may potentially provide useful information on guiding treatment choices in patients with ER+/HER2- mBC harboring *ESR1* mutations

Disclosures

- **MAC** has done consulting for Menarini, Eli Lilly, AstraZeneca, Ellipses, Celcuity, Olaris, and Sermonix; has received research support from Pfizer, Eli Lilly and AstraZeneca; and honoraria from Pfizer, Eli Lilly, Foundation Medicine, and Guardant. **DGS** is on the advisory board for Novartis. **HSR** has received research support from Pfizer, Merck, Novartis, Eli Lilly, Roche, Daiichi, Seattle Genetics, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AstraZeneca, Ayala, Astellas and Gilead and honoraria from Puma, Samsung, and NAPO. **EH** has receive research support (paid to institution) from Abbvie. Acerta Pharma, Accutar Biotechnology, ADC Therapeutics, AKESOBIO Australia, Amgen, Aravive, ArQule, Artios, Arvinas, AstraZeneca, AtlasMedx, Black Diamond, Bliss BioPharmaceuticals, Boehringer Ingelheim, Cascadian Therapeutics, Clovis, Compugen, Cullen-Florentine, Curis, CytomX, Daiichi Sankyo, Dana Farber Cancer Inst, Dantari, Deciphera, Duality Biologics, eFFECTOR Therapeutics, Eli Lilly, Ellipses Pharma, Elucida Oncology, EMD Serono, Fochon, FujiFilm, G1 Therapeutics, H3 Biomedicine, Harpoon, Hutchinson MediPharma, Immunogen Immunomedics, Incyte, Infinity Pharmaceuticals, InvestisBio, Jacobio, Karyopharm, Leap Therapeutics, Lycera, Mabspace Biosciences, Macrogenics, MedImmune, Merck, Mersana, Merus, Millennium, Molecular Templates, Myraid Genetic Laboratories, Novartis, Nucana, Olema, OncoMed, Onconova Therapeutics, ORIC Pharmaceuticals, Orinove, Pfizer, PharmaMar, Pieris Pharmaceuticals, Pionyr Immunotherapeutics, Plexxikon, Radius Health, Regeneron, Relay Therapeutics, Repertoire Immune Medicine, Rgenix, Roche/Genentech, SeaGen, Sermonix, Shattuck Labs, Silverback, StemCentRx, Sutro, Syndax, Syros, Taiho, Taplmmune Tesaro, Tolmar, Torque Therapeutics, Treadwell Therapeutics, Verastem, Vincerx Pharma, Zenith Epigenetics, Zymeworks; is a consultant/advisor (paid to institution) for Arcus, Arvinas, AstraZeneca, Black Diamond, Boehringer Ingelheim, CytomX, Daiichi Sankyo, Dantari, Deciphera, Eisai, Eli Lilly, Greenwich LifeSciences, H3 Biomedicine, iTeos, Janssen, Loxo, Merck, Mersana, Novartis, Orum Therapeutics, Pfizer, Propella Therapeutics, Puma Biotechnology, Relay Therapeutics, Roche/Genentech, SeaGen, Silverback Therapeutics. **TJP** is a consultant for AstraZeneca, Gilead, Hibercell, Novartis, Pfizer, Sanofi and Seagen; has received research support from AstraZeneca, Gilead, Hibercell, Novartis, Pfizer, Sanofi, Nuvation, and Olema; has been a speaker for AstraZeneca, Gilead, and Seagen. **DPMc** is a licensed IP with Elascestrant (Radius health/Menarini) and Sermonix (Lasofoxifene); a consultant for Bristol Myers Squibb, Zentalis, X-Rad Therapeutics, and RAPPT Therapeutics; has received research support from Bristol Myers Squibb, Zentalis, and Ribometrix. **DC** and **BK** are consultants for Sermonix. **PVP** and **DJP** are employees/stockholders of Sermonix.
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